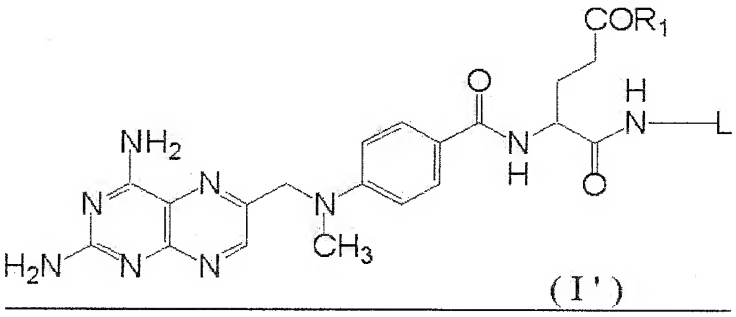
Amendments to the Claims

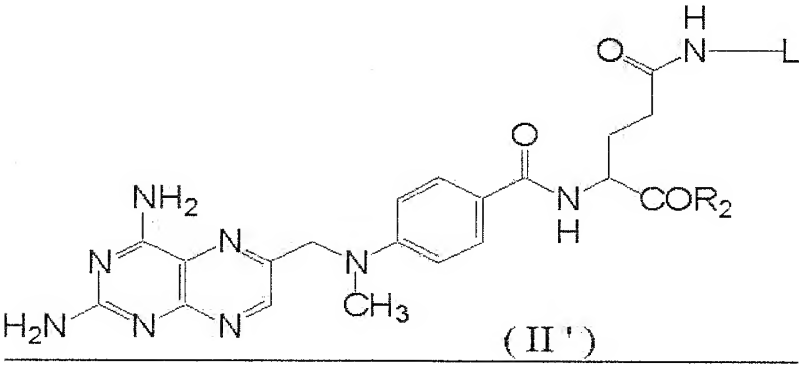
This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A hyaluronic acid-methotrexate conjugate, wherein methotrexate is conjugated with a carboxyl group of hyaluronic acid, a hyaluronic acid derivative, or a salt thereof through a linker containing a peptide chain consisting of 1 to 8 amino acids; or a salt of the conjugate, wherein the linker containing a peptide chain and methotrexate conjugated with the linker is represented by formula (I') or (II'):



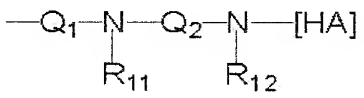
(I')



(II')

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a C_{1-6} alkoxy group, a C_{1-6} alkylamino group, or a di-C_{1-6} alkylamino group;

L is a linker represented by formula (x):



(X)

wherein Q_1 forms, together with -NH- binding thereto, a peptide chain consisting of 1 to 8 amino acids; residues of amino acids contained in the peptide chain are each independently optionally substituted or protected by one or more groups selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a formyl group, a C_{1-6} alkylsulfonyl group, and a C_{6-10} arylsulfonyl group; amide bonds contained in the peptide chain are each independently optionally substituted on the nitrogen atom by one or more C_{1-6} alkyl groups and/or C_{1-6} alkylcarbonyl groups; and carboxyl groups contained in the residues are each independently optionally converted to an amide group optionally substituted by one or two C_{1-6} alkyl groups;

R_{11} and R_{12} are each independently a hydrogen atom or a C_{1-6} alkyl group;

Q_2 is C_{2-20} alkylene, wherein the alkylene optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a carboxyl group or a C_{1-6} alkoxycarbonyl group; and

[HA] represents the position of conjugation with the hyaluronic

acid, derivative, or salt thereof, and the linker forms an amide bond with a carboxyl group contained in the hyaluronic acid, derivative or salt thereof.

2. (**Cancelled**)

3. (**Currently Amended**) The hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1 ~~or 2~~, wherein the conjugation rate of methotrexate is 0.5% to 4.5% based on the total carboxyl groups of hyaluronic acid.

4. (**Previously Presented**) The hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1 , wherein the molecular weight of hyaluronic acid is 600,000 daltons or more.

Claims 5 and 6. (**Cancelled**)

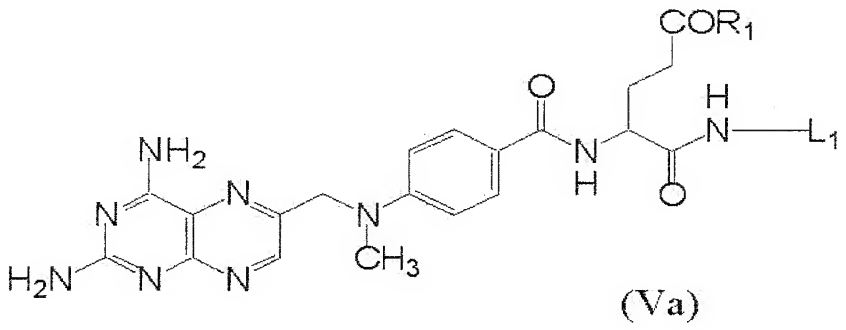
7. (**Previously Presented**) A pharmaceutical composition containing the hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1 as an active ingredient.

8. (**Previously Presented**) A therapeutic drug for joint diseases, containing the hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1 as an active ingredient.

9. (**Original**) The therapeutic drug for joint diseases according to claim 8, which is a topical preparation for administration into the joint.

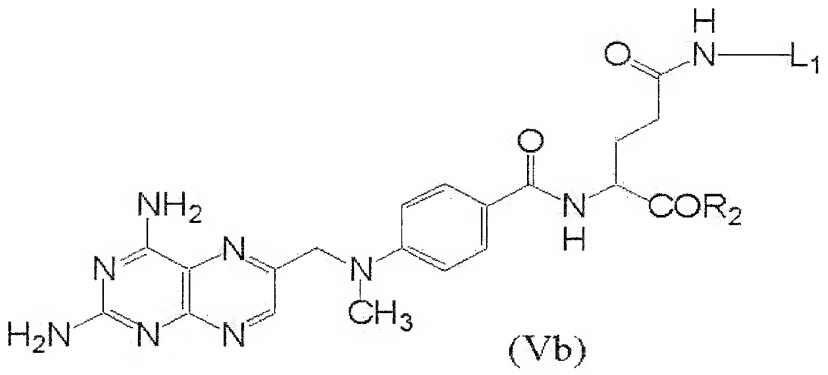
10. (**Previously Presented**) A compound of formula (Va) or (Vb):

[Formula 8]



(Va)

[Formula 9]

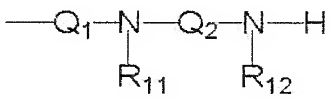


(Vb)

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a C_{1-6} alkoxy group, a C_{1-6} alkylamino group, or a di-C_{1-6} alkylamino group;

L_1 is a linker represented by formula (X'):

[Formula 10]



(X')

wherein Q_1 forms, together with -NH- binding thereto, a peptide chain consisting of 1 to 8 amino acids; residues of amino acids contained in the peptide chain are each independently optionally substituted or protected by one or more groups selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a formyl group, a C_{1-6} alkylsulfonyl group, and a C_{6-10} arylsulfonyl group; amide bonds contained in the peptide chain are each independently optionally substituted on the nitrogen atom by one or more C_{1-6} alkyl groups and/or C_{1-6} alkylcarbonyl groups; and carboxyl groups contained in the residues are each independently optionally converted to an amide group optionally substituted by one or two C_{1-6} alkyl groups;

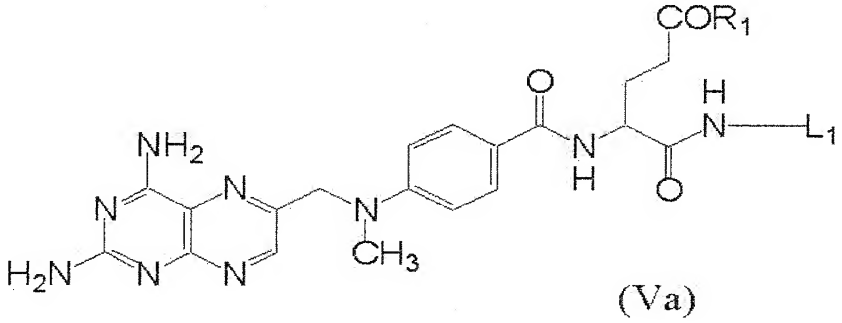
R_{11} and R_{12} are each independently a hydrogen atom or a C_{1-6} alkyl group; and

Q_2 is a C_{2-20} alkylene, wherein the alkylene optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a C_{1-6}

alkoxycarbonyl group.

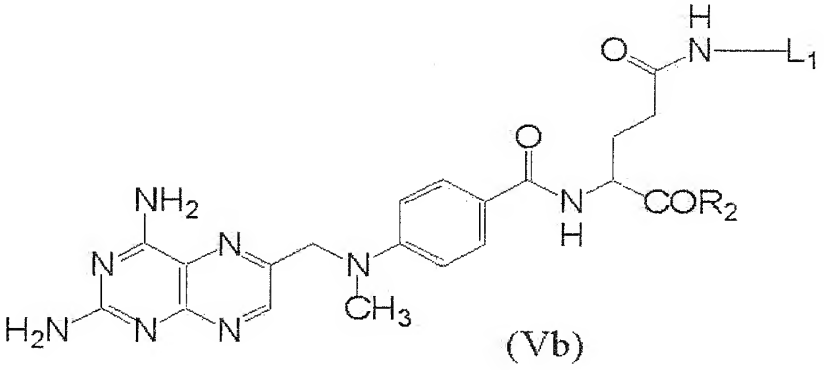
11. (**Previously Presented**) A process for producing the hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 1, which comprises the steps of reacting the compound of formula (Va) or (Vb) with hyaluronic acid, a hyaluronic acid derivative, or a salt thereof, and converting a carboxyl group of the hyaluronic acid, derivative, or salt thereof to an N-substituted amide group, wherein (Va) and (Vb) are as follows:

[Formula 8]



(Va)

[Formula 9]



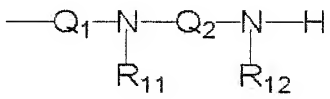
(Vb)

wherein R_1 and R_2 are each independently a hydroxy group, an amino group, a C_{1-6} alkoxy group, a C_{1-6} alkylamino group, or a di-C_{1-6} alkylamino

group;

L_1 is a linker represented by formula (X'):

[Formula 10]



(X')

wherein Q_1 forms, together with -NH- binding thereto, a peptide chain consisting of 1 to 8 amino acids; residues of amino acids contained in the peptide chain are each independently optionally substituted or protected by one or more groups selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, a formyl group, a C_{1-6} alkylsulfonyl group, and a C_{6-10} arylsulfonyl group; amide bonds contained in the peptide chain are each independently optionally substituted on the nitrogen atom by one or more C_{1-6} alkyl groups and/or C_{1-6} alkylcarbonyl groups; and carboxyl groups contained in the residues are each independently optionally converted to an amide group optionally substituted by one or two C_{1-6} alkyl groups;

R_{11} and R_{12} are each independently a hydrogen atom or a C_{1-6} alkyl group; and

Q_2 is a C_{2-20} alkylene, wherein the alkylene optionally has 1 to 5 oxygen atoms inserted thereinto and/or is optionally substituted by a carboxyl group or a C_{1-6} alkoxycarbonyl group.

12. (**Cancelled**)

13. (**Previously Presented**) The hyaluronic acid-methotrexate conjugate or the salt thereof according to claim 3, wherein the molecular weight of hyaluronic acid is 600,000 daltons or more.

Claims 14-17. (**Cancelled**)